Armed Forces College of Medicine

AFCM

Applied Biochemistry (1)

Neuroscience Module

INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

1- Illustrate the major biochemical pathways for neurotransmitter synthesis and degradation

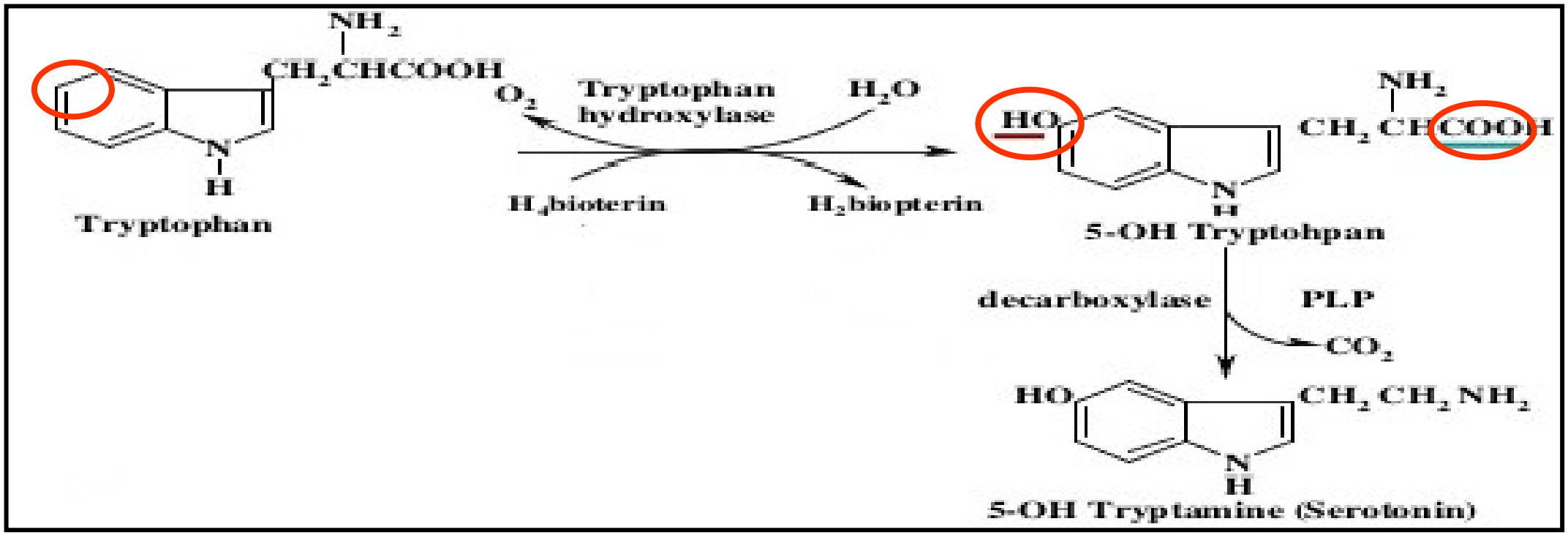
3- Illustrate the reactions of urea cycle

4- Explain the biochemical basis of homocystinuria, phenylketonuria, maple syrup urine disease and sphingolipidoses

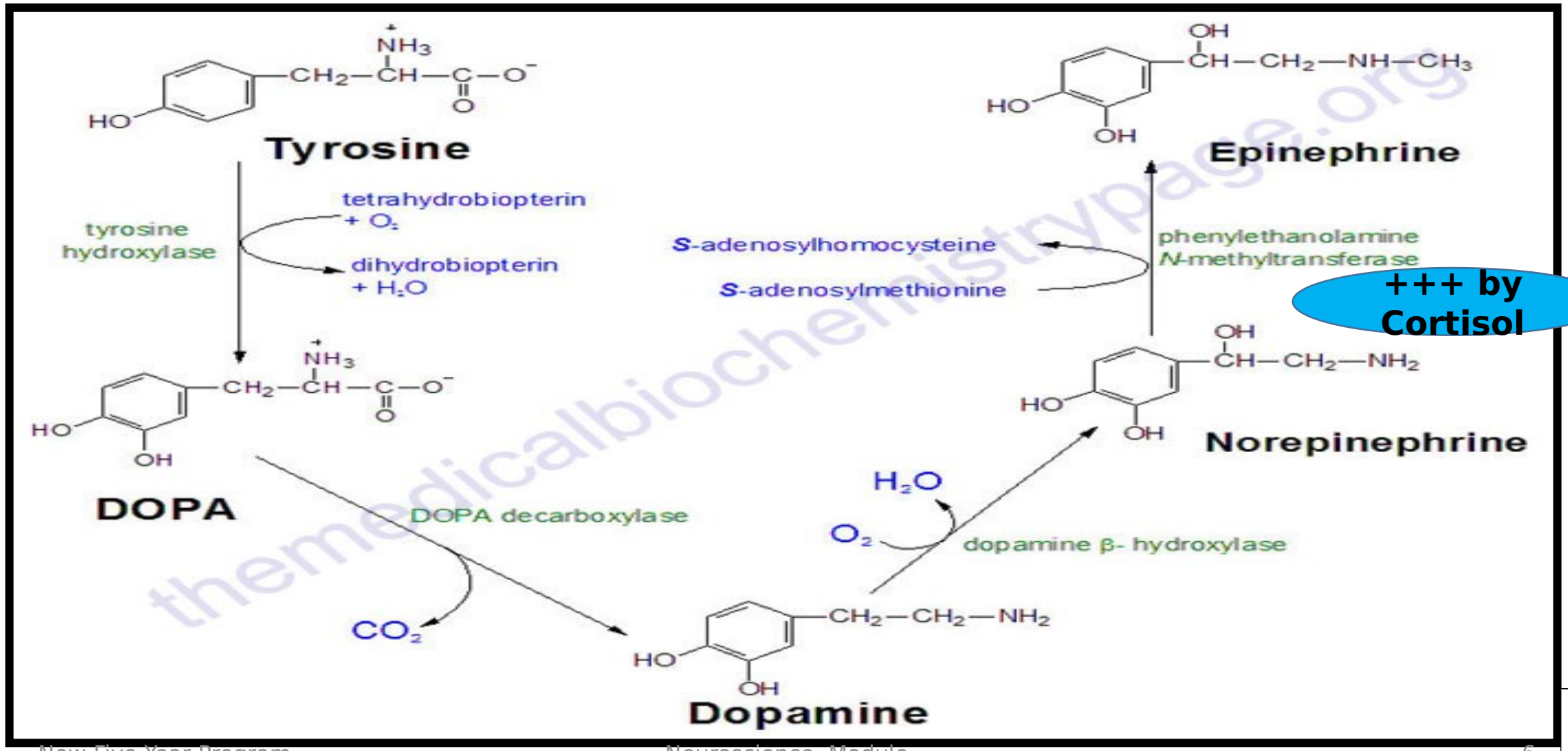
Outline the conversion of:

1) Tryptophan to serotonin
2) Tyrosine to epinephrine

1) Biosynthesis of Serotonin



2) Synthesis of catecholamines



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The rate limiting step in the biosynthesis of catecholamines is

(A) Decarboxylation of dihydroxyphenylalanine
(B) Hydroxylation of phenylalanine
(C) Hydroxylation of tyrosine
(D) Oxidation of dopamine
(E) Decarboxylation of DOPA

The enzyme dopamine β-hydroxylase which catalyses conversion of dopamine to norepinephrine requires

(A) Vitamin A

(B) Vitamin C

(C) Vitamin E

(D) Vitamin B12

(E) Vitamin K

Match the following

(N.B more than one answer is possible)

1) Serotonin

2) Dopamine

3) Epinephrine

A) Monoamine oxidase (MAO)

B) Catechol-O-Methyl Transferase (COMT)

C) 5-hydroxyindolacetic acid (5-HIAA)

D) Homovanillic acid (HVA)

E) Vanillylmandelic acid (VMA)

Explain on biochemical basis

1) L-dopa is used in treatment of Parkinson disease

2) α-methyl dopa is used in treatment of hypertension

3) Vitamin B6 deficiency causes convulsions

Explain on biochemical basis

L-dopa is used in treatment of Parkinson disease

Parkinson disease:

- A neurodegenerative movement disorder, due to deficiency of Dopamine in the brain

- L-dopa (precursor of dopamine) is used in the treatment of parkinsonism as it can cross the blood brain barrier.

- Dopamine cannot.

Explain on biochemical basis

α-methyl dopa is used in treatment of hypertension

as it can competitively inhibit DOPA decarboxylase enzyme

Explain on biochemical basis

Vitamin B6 deficiency causes convulsions

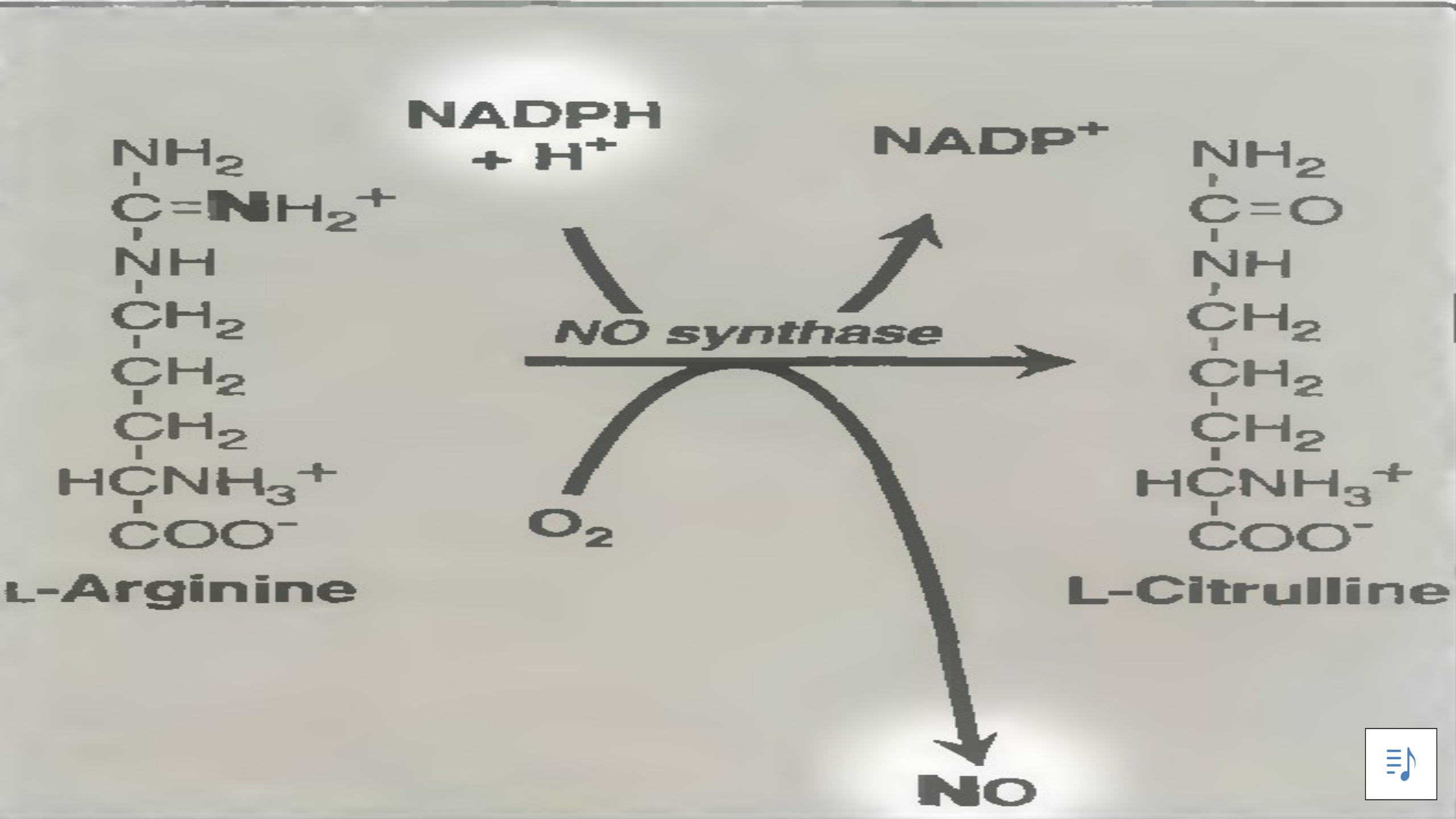
Due to deficiency of pyridoxal phosphate, the coenzyme of glutamic acid decarboxylase (GAD) enzyme which catalyzes the synthesis of the inhibitory neurotransmitter (GABA)

Nitric oxide is a bioactive molecule having multifunctional aspects in human body.

1) Describe the synthesis of nitric oxide.

2) Enumerate the functions of nitric oxide.

3) Explain the use of nitric oxide as a therapeutic agent.


NADPH
+ H+
NADP+
NO synthase
O2
NO
L-Arginine
L-Citrulline

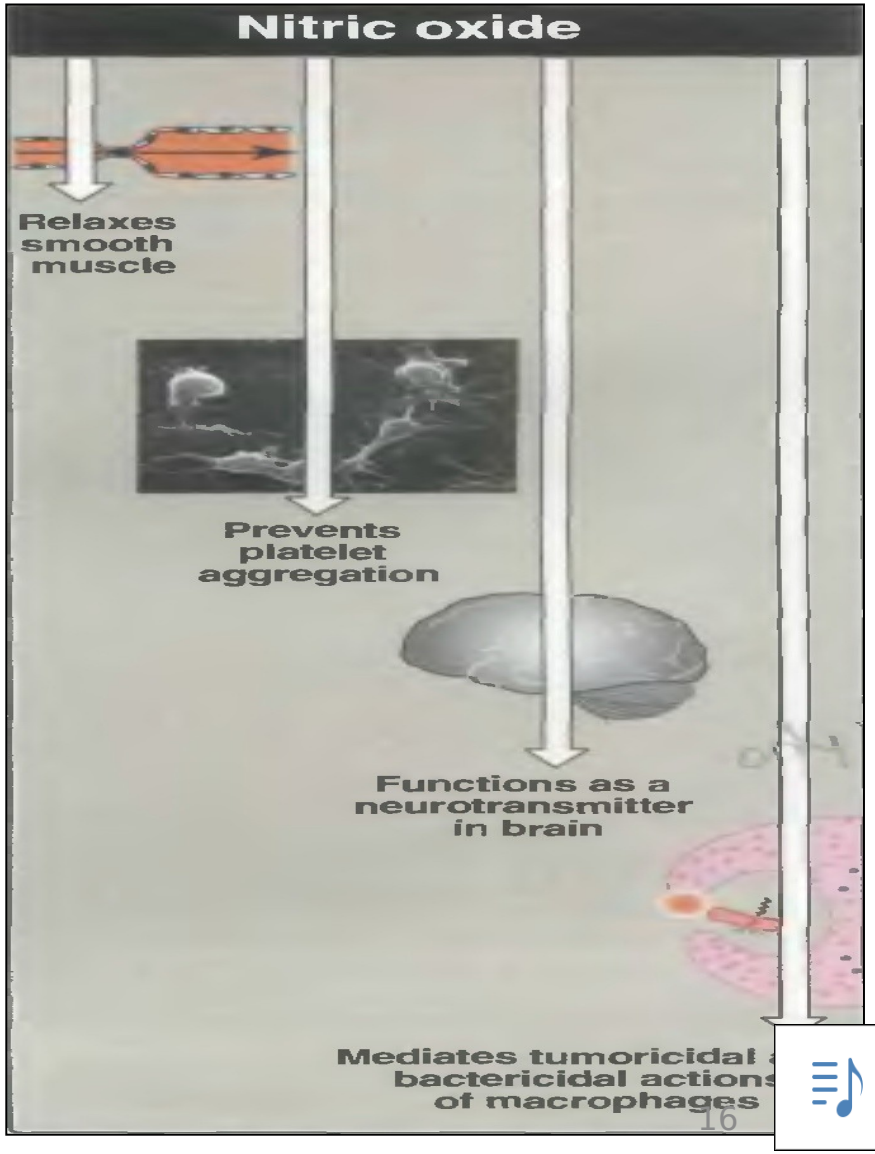
Functions of NO:

-Is a potent vasodilator of cerebral, coronary and muscles arteries.

-It relaxes smooth muscles of GIT and urogenital tract by acting as a neurotransmitter.

-It stimulates release of (CRH), (GHRH) and (LHRH) from hypothalamus.

-It is produced by macrophages, monocytes and neutrophils to kill

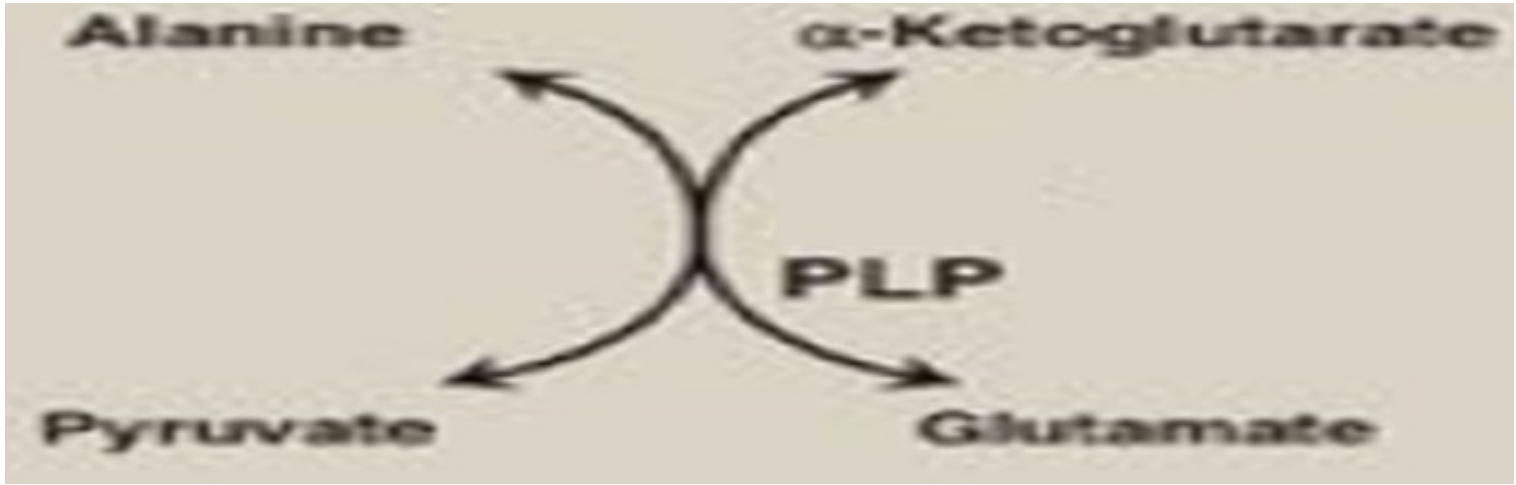


Pharmacological functions of NO:

1-Nitroglycerin is used in the treatment of angina.

2-Inhalation of NO can be used in the treatment of pulmonary hypertension and high altitude pulmonary edema.

Mention the name of the enzyme catalyzing the following reaction



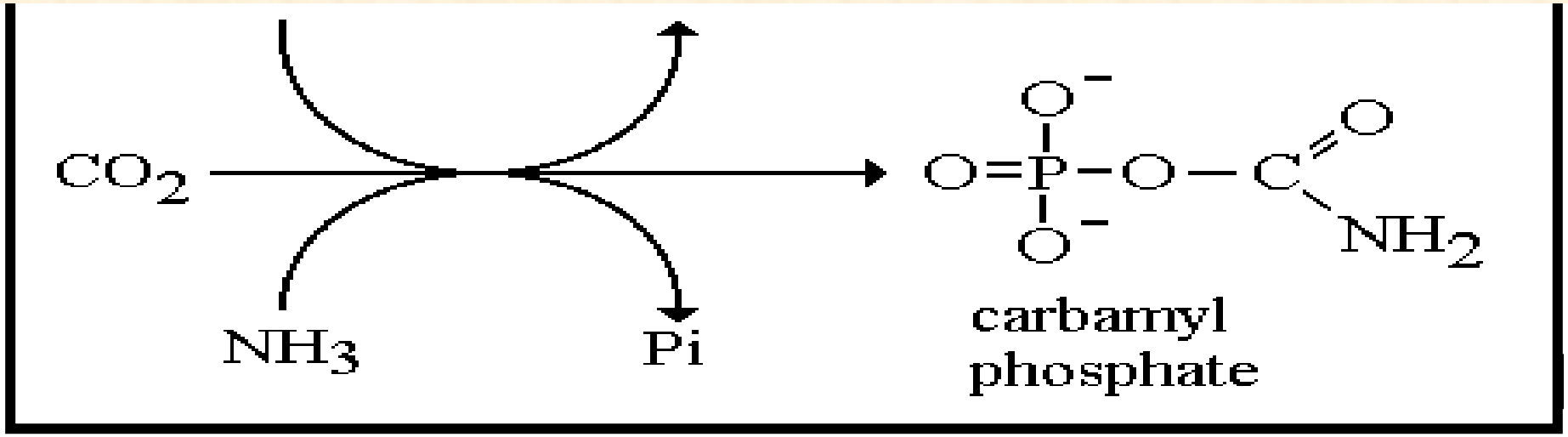
Alanine aminotransferase (ALT)
or
Glutamic pyruvic transaminase (GPT)

Mention the name of the enzyme catalyzing the following reaction

Glutamate dehydrogenase enzyme

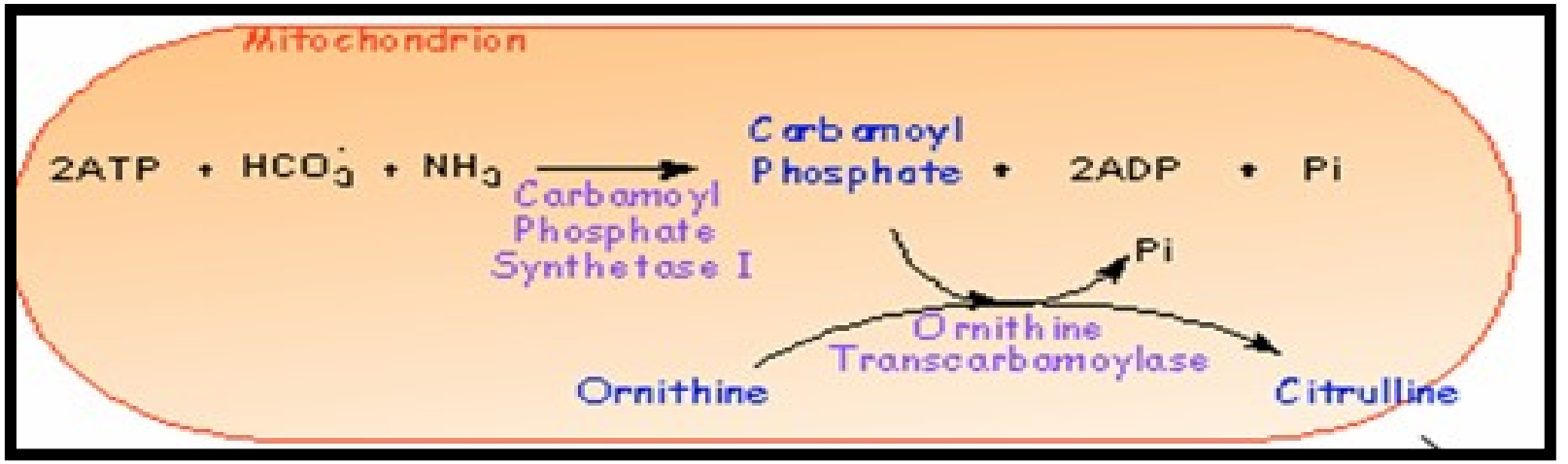
Illustrate two mitochondrial reactions of urea synthesis

1) Biosynthesis of carbamoyl phosphate



- This energy
(CO2 is a product of citric acid cycle, ammonia is derived from glutamate by deamination, the phosphate and energy are derived from ATP).
- It is catalyzed by mitochondrial carbamoyl phosphate synthetase I (CPS I) (the rate-limiting enzyme of urea cycle).
- 2 ATPs are required.

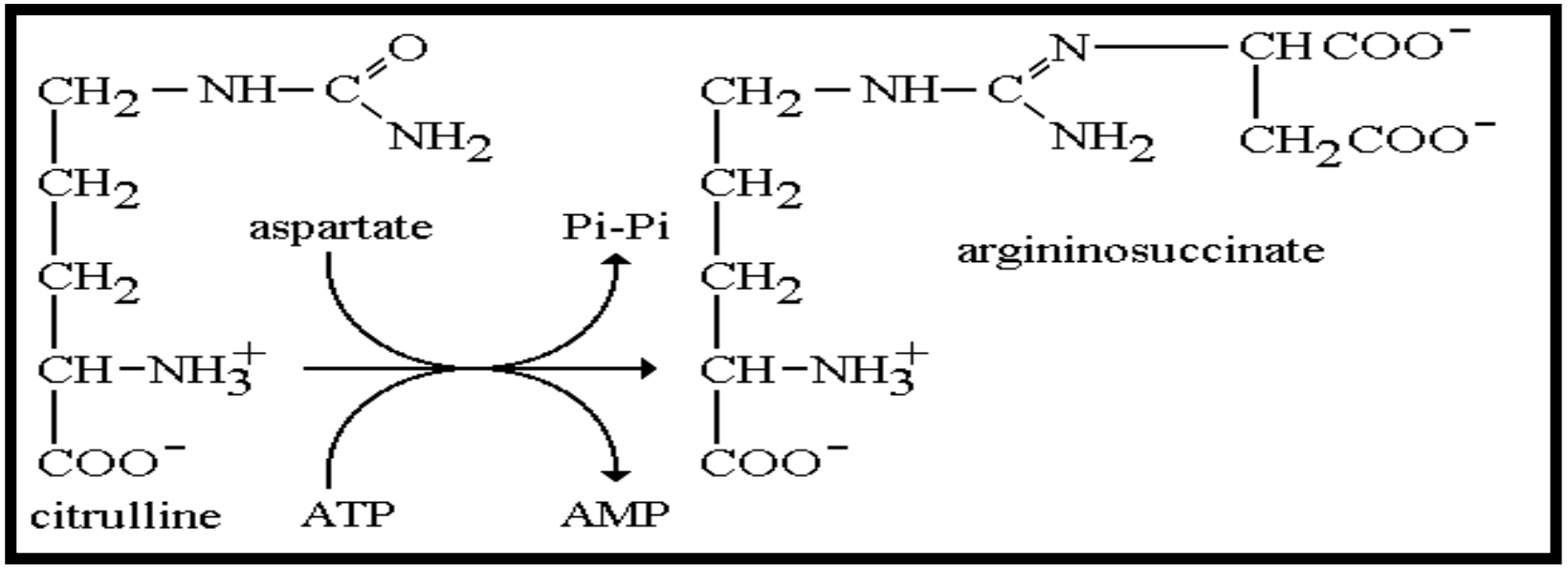
2- Formation of citrulline



The carbamoyl portion of carbamoyl phosphate is transferred to ornithine by ornithine transcarbamoylase (OTC) and the high-energy phosphate is released as inorganic phosphate. The reaction product, citrulline, is transported to the cytosol.

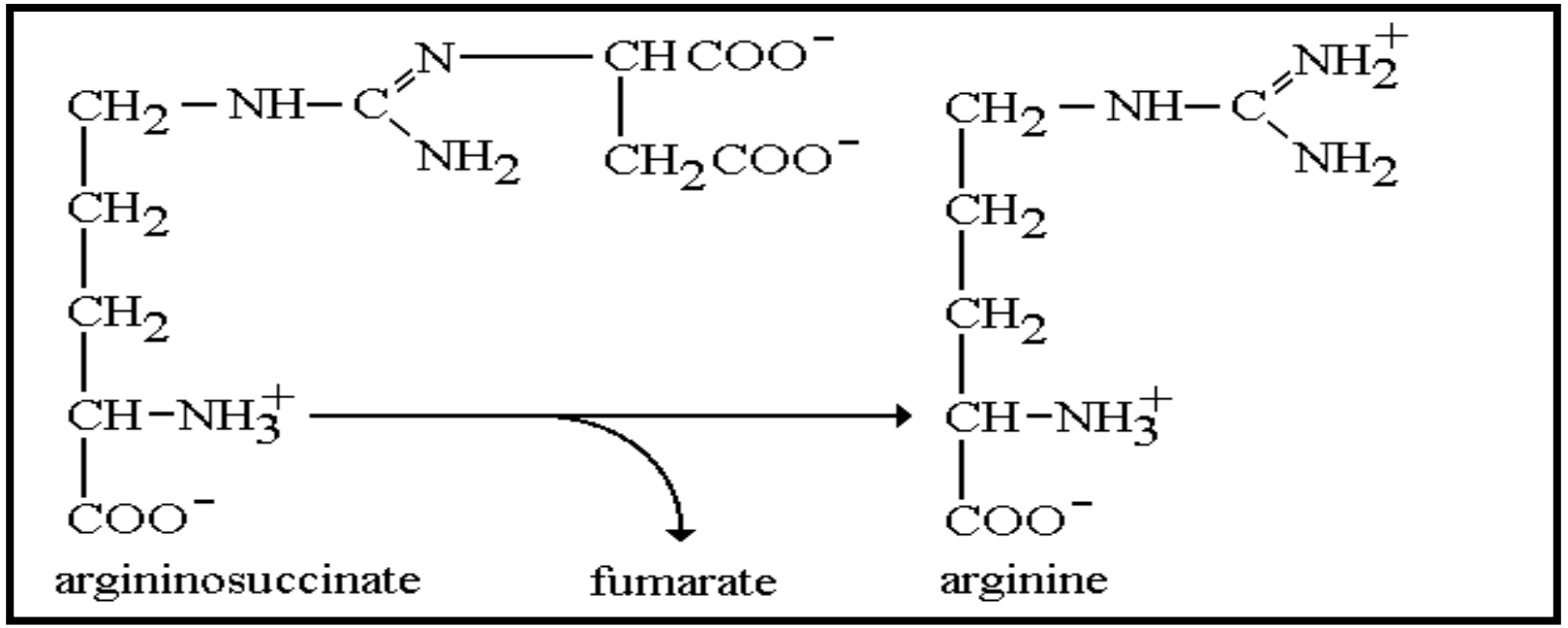
Illustrate three cytosolic reactions of urea synthesis

3- Formation of argininosuccinate



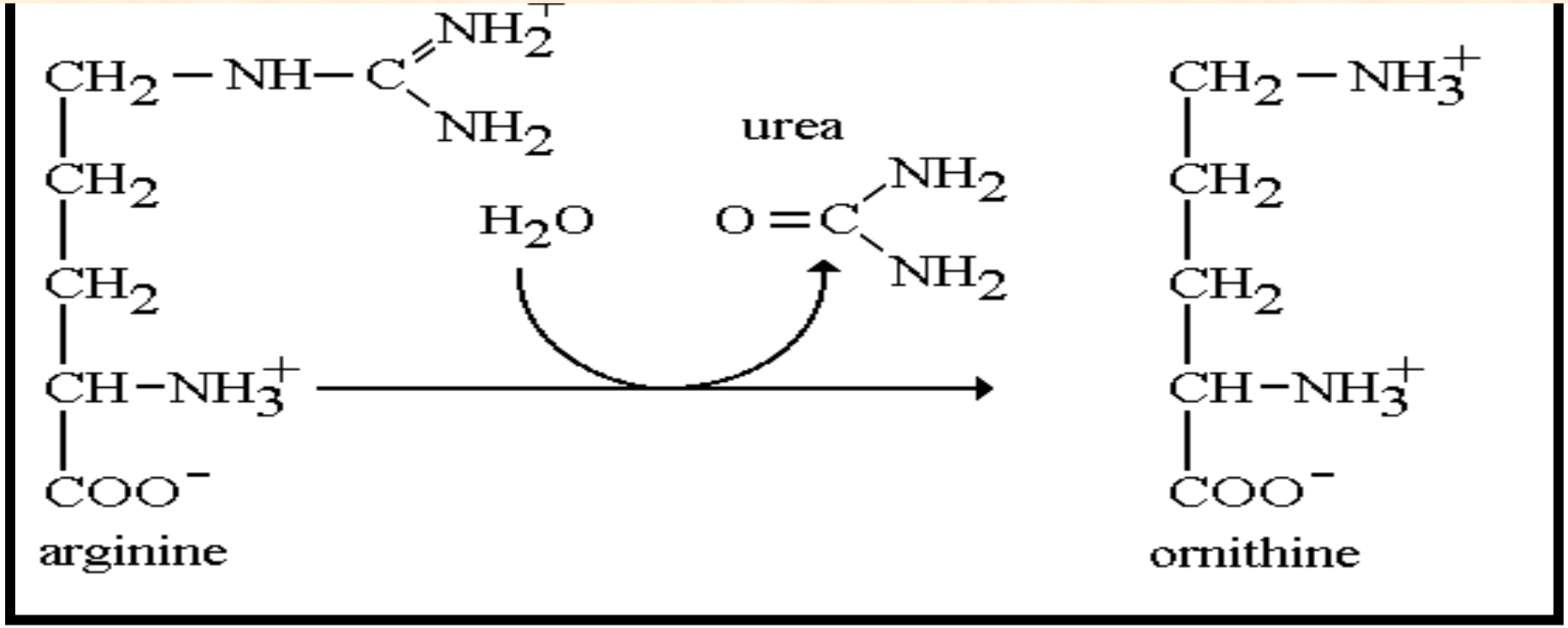
- One molecule of aspartic acid is added to citrulline forming argininosuccinate which provides the 2nd N of urea.
- Catalyzed by argininosuccinate synthetase

4- Cleavage of argininosuccinate



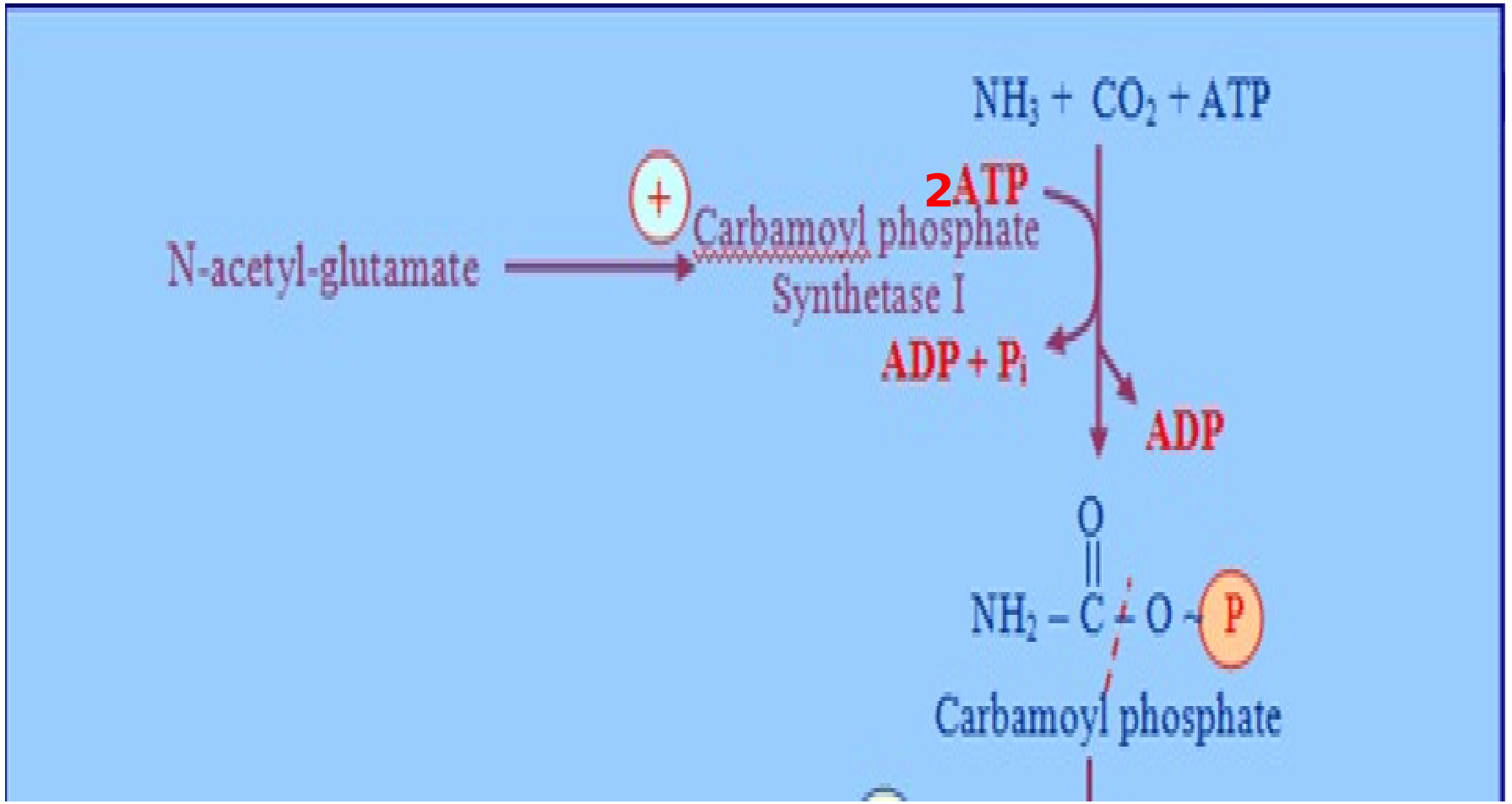
Argininosuccinate is cleaved by argininosuccinate lyase to yield arginine and fumarate

5- Cleavage of arginine by arginase into urea and ornithine



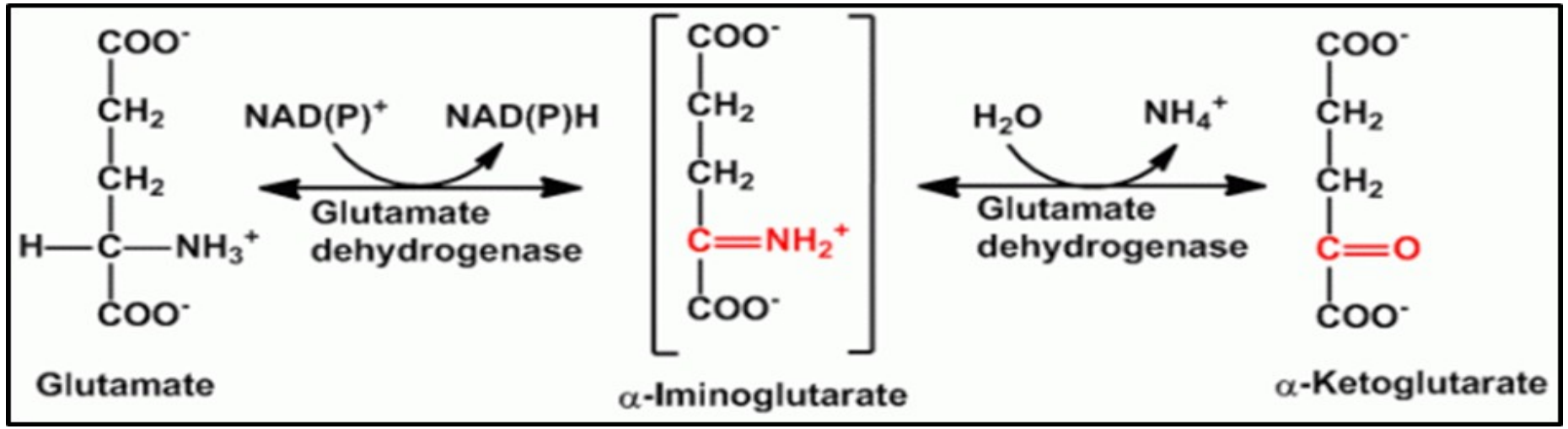
N.B Ornithine and citrulline are basic amino acids that participate in the urea cycle, moving across the inner mitochondrial membrane via a cotransporter.

Illustrate the key regulatory step in urea synthesis



Mention the effect of ammonia on energy production in brain cells

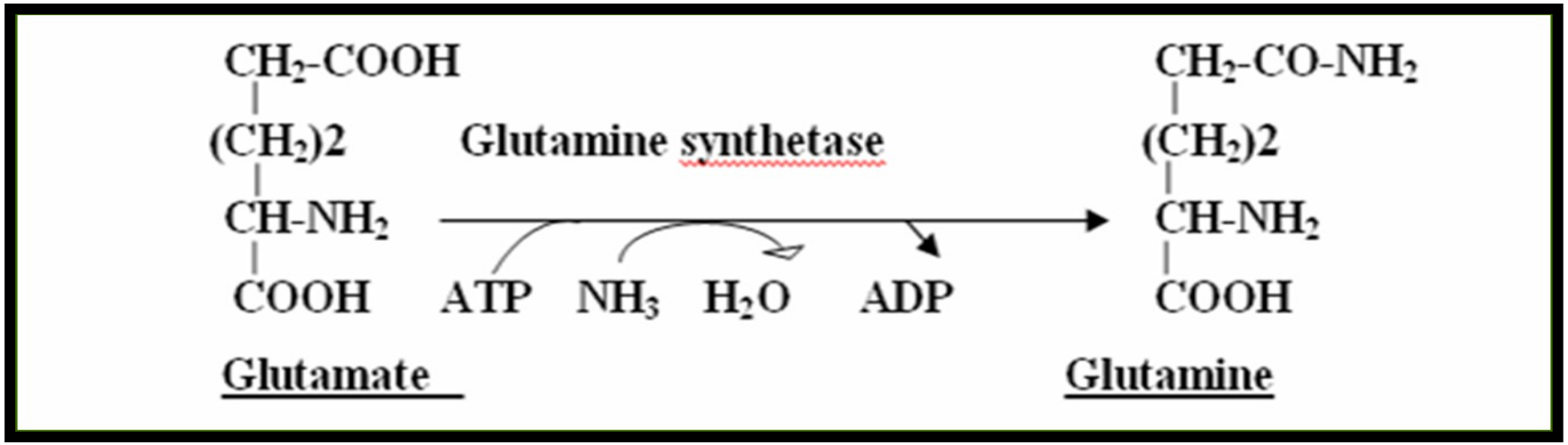
The level of α-KG is reduced



Shortage in TCA-cycle and ↓ ATP generation which is required for various brain activities

Explain the effect of increased ammonia on neurotransmitters production

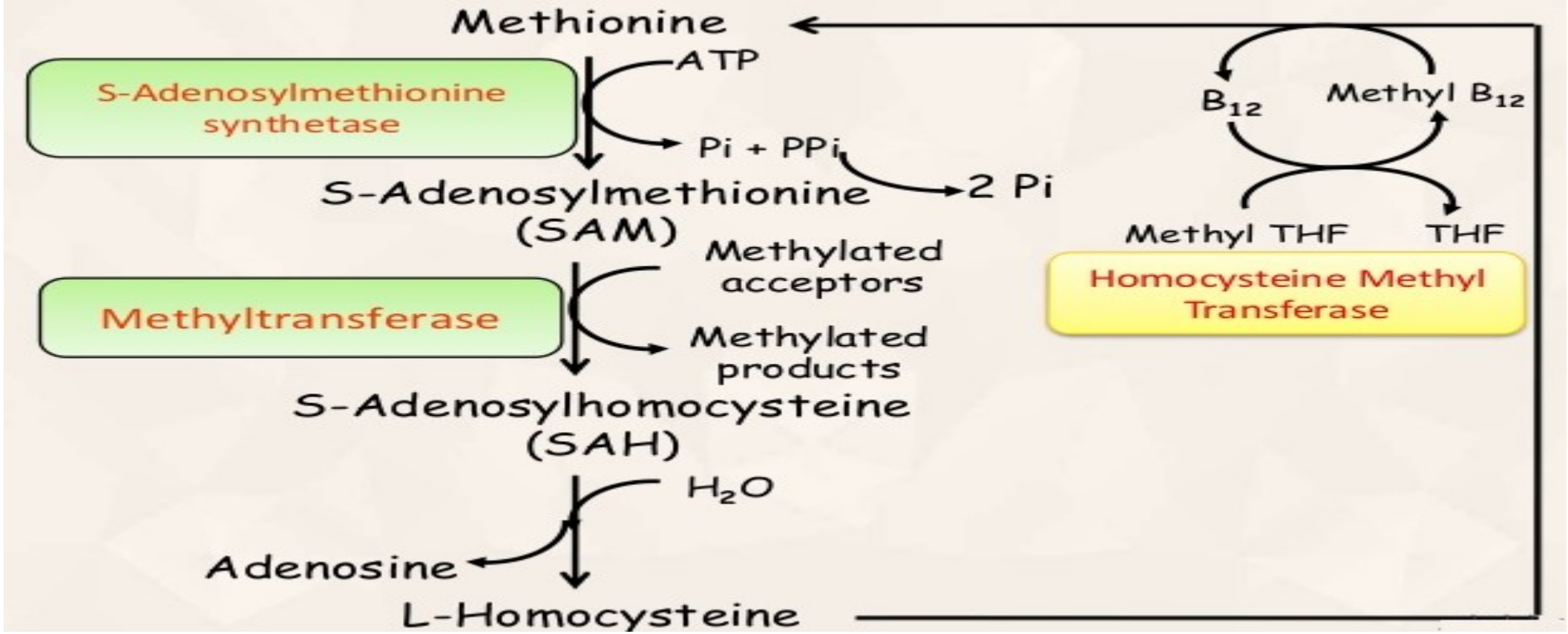
1) Depletion of glutamate in brain (to form glutamine)



Depletion of glutamate leads to decrease production of GABA

2) Excess glutamine is exchanged with Tryptophan a precursor for serotonin (Excitatory neurotransmitter)

Illustrate the reaction catalyzed by Homocysteine methyl transferase and outline its clinical significance

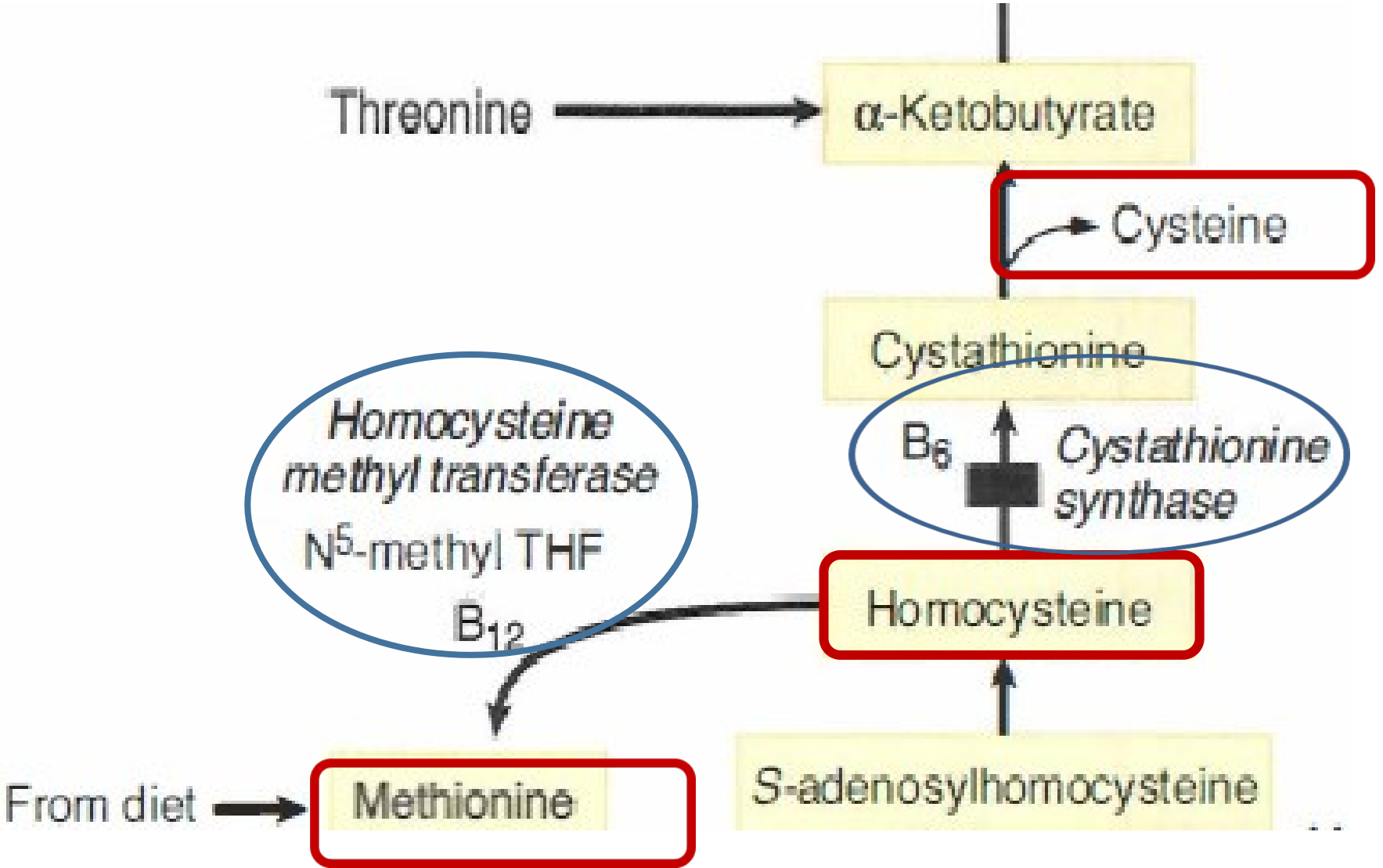


Clinical significance

Deficiency of homocysteine methyl transferase enzyme

Homocystinuria

Metabolism of homocysteine



Deficiency of the following vitamin can cause homocystinuria:

a)Niacin

b)Pyridoxal phosphate

c)B12

d)A&B

e)B&C

Homocystinuria

1) due to defect in cysteine synthesis due to:

A-Deficiency of cystathionine synthase or cystathionase

B-Deficiency of PLP

2) Defect in conversion of homocysteine to methionine due to deficiency of:

A- Folic acid

B- Vitamin B12

C- Homocysteine methyl transferase

Clinical picture

1) **Coronary heart disease: due to atherogenic effect of homocysteine.**
2) **Weak extracellular matrix: homocysteine binds to lysine of collagen and prevents cross linking.**

Manifested by:

a) **mental retardation**
b) **Bone deformities**
c) **Dislocation of the lens.**

3) **Thrombosis: the major cause of early death in these individuals.**

Treatment

A) Defect in cysteine synthesis:

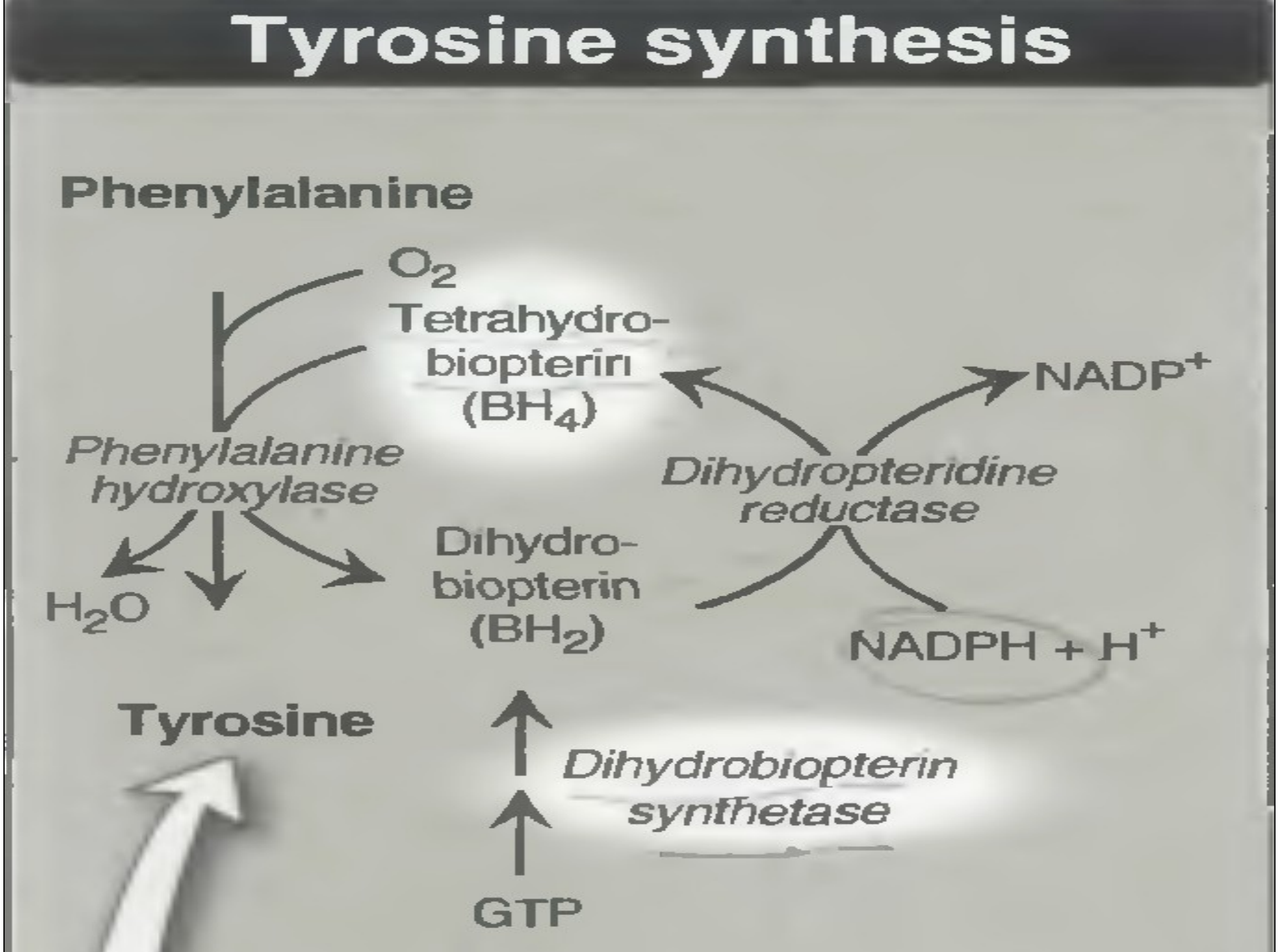
1) Supplementation of cysteine
2) pyridoxine (vitamin B6), which is converted to pyridoxal phosphate

B) Defect in regeneration of methionine:

3) Decrease methionine in diet
4) Supplementation of folic acid or vitamin B12
5) Supplementation of choline as methyl donor.

Illustrate the reaction catalyzed by phenylalanine hydroxylase and outline its clinical significance

Tyrosine synthesis

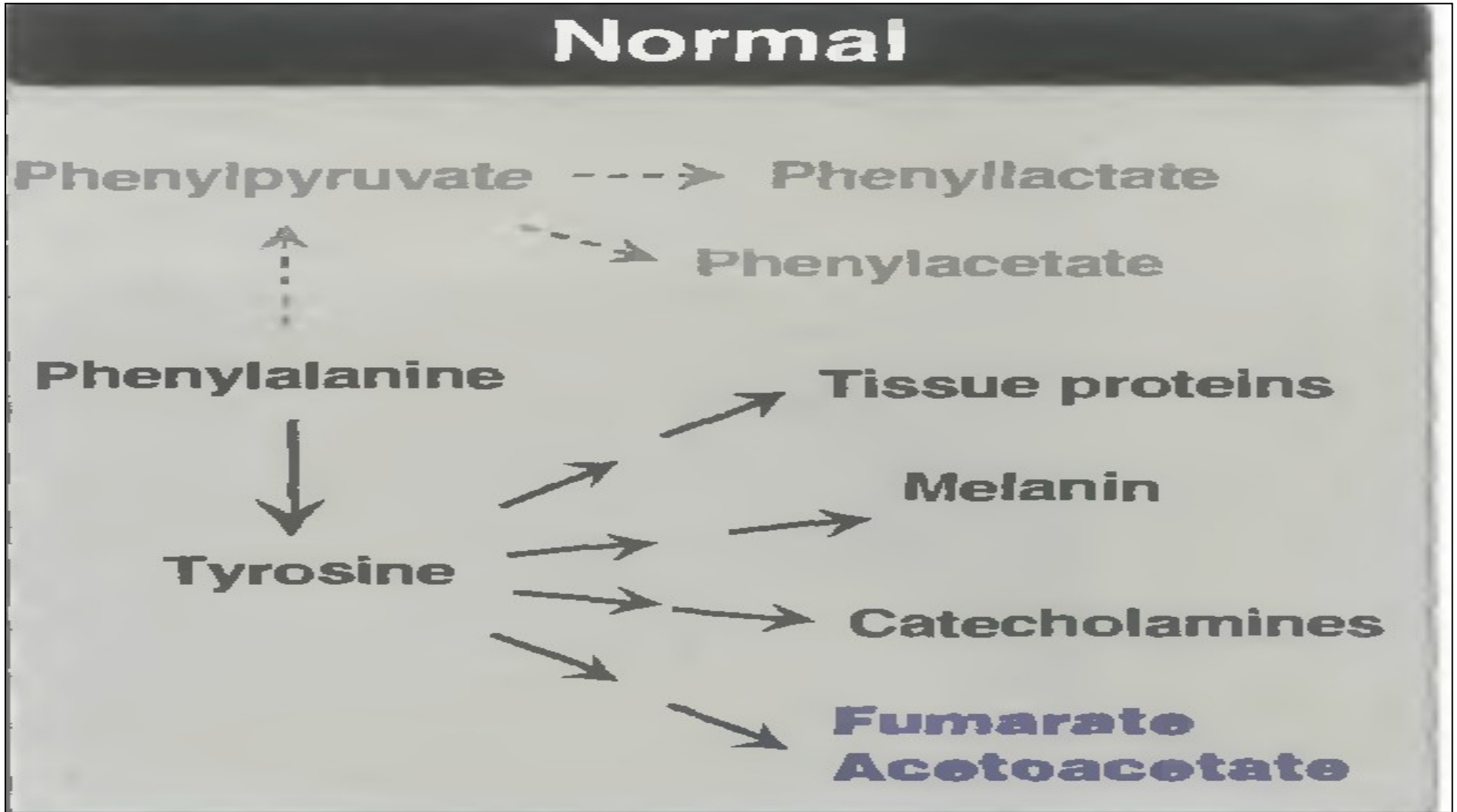


Clinical significance

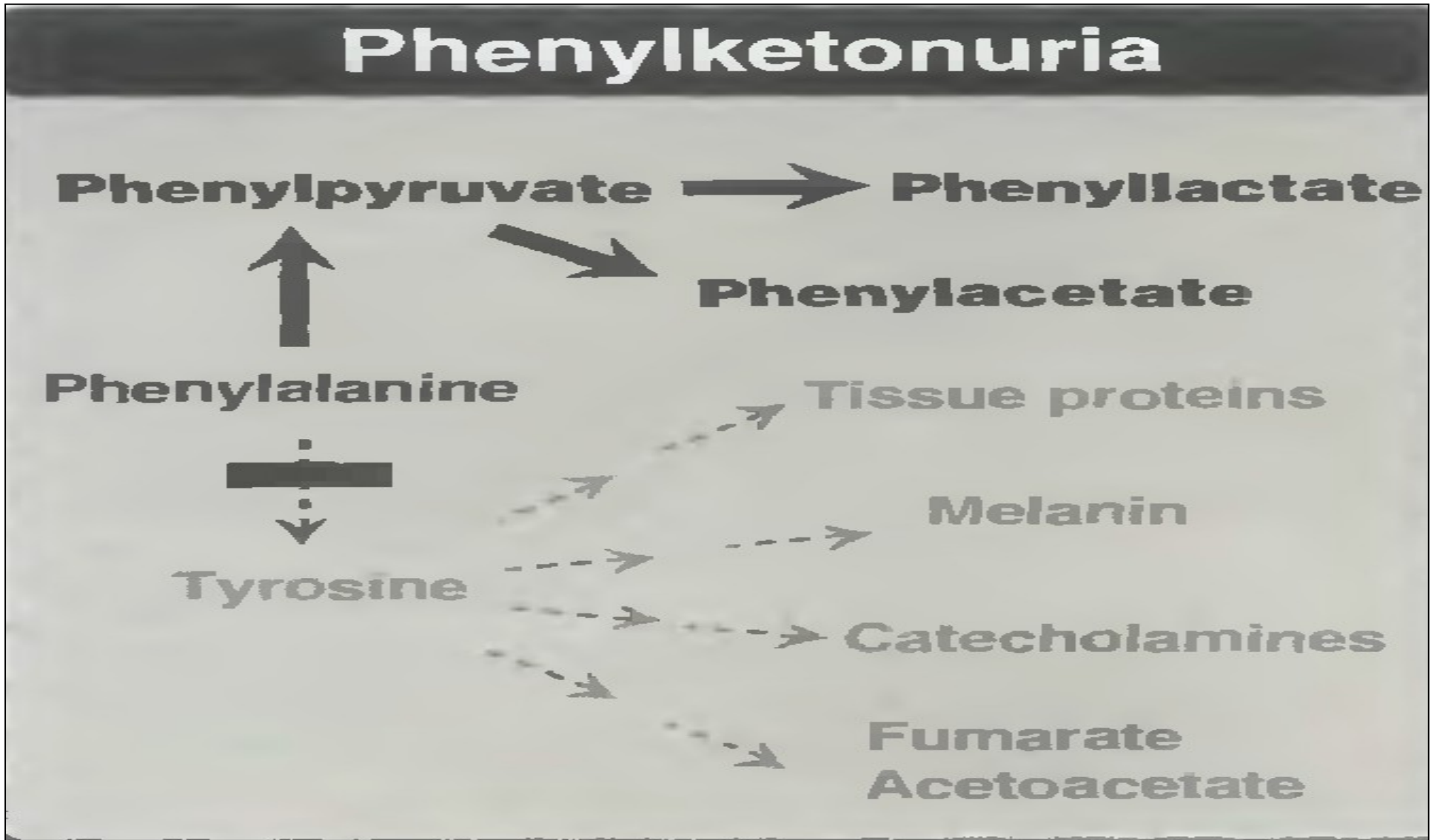
Deficiency of phenylalanine hydroxylase enzyme

Phenylketonuria

Phenylalanine



Phenylketonuria



Clinical picture:

1) CNS symptoms:

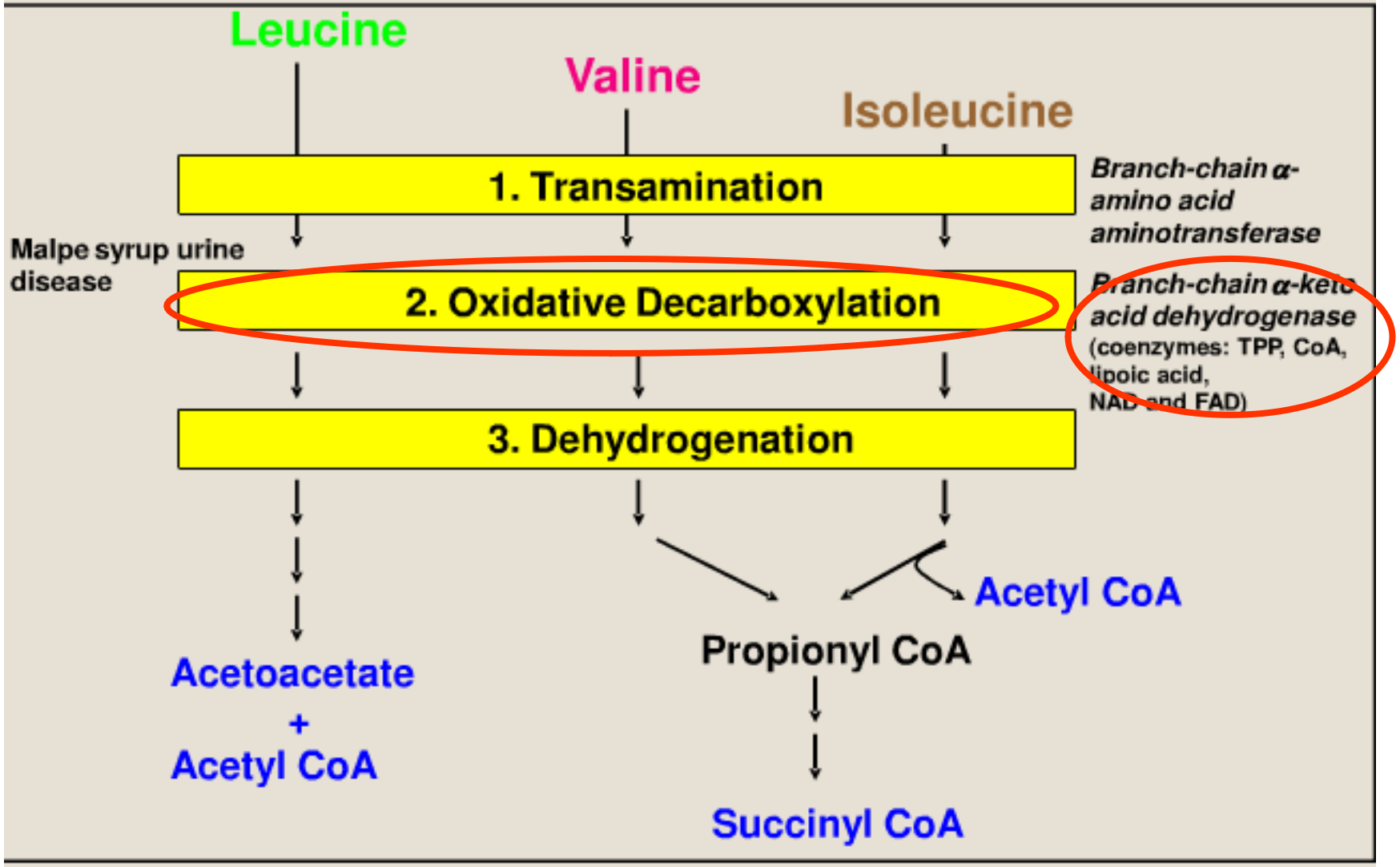
Severe intellectual delay (mental retardation) due to deficiency of brain catecholamines and accumulation of toxic products in tissues. These toxic products are derived from abnormal metabolism of phenylalanine.

2) Depigmentation: due to↓ melanin synthesis.

3) Urine: bad mousy odor caused by abnormal metabolites.

Illustrate the reaction catalyzed by Branched chain α keto acids dehydrogenase complex and outline its clinical significance

Branched-chain Amino Acids Catabolism



Maple Syrup Urine Disease

- **It results from deficiency of the dehydrogenase complex which catalyzes the oxidative decarboxylation step.**
- **The branched chain α-AAs and their corresponding α-keto acids accumulate in blood causing a toxic effect that interferes with brain functions.**
- **The disease is characterized by mental retardation and may lead to early death.**
- **The urine has a sweet smell-like maple syrup or burned sugar due to rise in isoleucine.**
- **TTT: diet low in branched α-AAs**

Thank you